AMENDMENT

In the claims:

Please amend claims 1 and 2, so that the text of the amended claims reads as follows.

A1

1.(Amended) An isolated nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1.

2.(Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

Please add new claims 7-8.

A2

--7.(New) An expression vector comprising a nucleic acid sequence of Claim 1.

8.(New) A cell comprising the expression vector of Claim 7.--

RESPONSE

I. Status of the Claims

No claims have been canceled. Claim 1and 2 have been amended. New claims 7 and 8 have been added. Claims 1-8 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. In compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit B**.

II. Support for the Claims

Claim 1 has been amended to further clarify the claim. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in Claim 1 as originally filed.

Claim 2 has been amended to further clarify the claim, and to recite specifically highly stringent hybridization conditions. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in Claim 2 as originally filed.

New Claim 7 has been added to more clearly claim certain aspects of the invention. Claim 7 finds support throughout the specification as originally filed, with particular support being found at least at page 10, lines 26-32.

New Claim 8 has been added to more clearly claim certain aspects of the invention. Claim 8 finds support throughout the specification as originally filed, with particular support being found at least at page 10, line 32-page 11, line5.

As the amendments to claims 1 and 2 and new claims 7 and 8 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry therefore is respectfully requested.

III. Objections

The Action objects to Claim 1 due to several alleged informalities. Claim 1 as amended is believed to have successfully addressed this issue.

IV. Rejection of Claims Under 35 U.S.C. § 101

The Action rejects claims 1-6 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility. Applicants respectfully traverse.

The present application describes novel members of the *Notch* ligand family. The Action recognizes this assertion (on page 8, line 7 of the last paragraph), but takes issue with Applicants assertion that shares structural similarity with SEL-1 in particular. The Action then goes on to note the differences between SEL-1 and the protein encoded by SEQ ID NO:2. These differences include low levels of homology and tissues in which the protein is expressed. Applicants concur that the invention is not identical to SEL-1(Accession Number Q9UBV2). Applicants submit that the protein of the present invention is significantly more similar, 99.8% identity over the506 amino acid overlap, to "Novel protein similar to SEL1L(Sel-1suppressor of lin-12, *C. elegans*)-like) (Accession Number Q9UGD3: **Exhibit C**) whose entire amino acid sequence in within the protein of the present invention.

As noted in the specification (page 14 lines 12-23):

Because of the diverse activities that have been associated with *Notch* signaling pathways, *Notch* receptors, and their associated ligands and antagonists have been subject to intense scientific scrutiny. For examples of how the described NHPs, or related *Notch* receptors can be produced, antagonized, used, processed, applied, and delivered, see, for example, U.S. Patent Nos. 5,786,158 and 5,780,300, and 5,856,441 the disclosures of which are hereby incorporated by reference in their entirety. Given their structural relatedness to *Notch* ligands, the described NHPs are suitable for use and modification as contemplated for other *Notch* ligands and antagonists.

The utility of *Notch* proteins and ligands is therefore well-known to the art.

As the protein of the instant invention belongs to a family of compounds with a common, well established specific and substantial utility, the Federal Circuit's ruling in *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is completely on point. In *Brana*, the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted.

The Examiner suggests that a "specific" utility might require further characterization (Action at page 6). However, even if, *arguendo*, further characterization might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of <u>further research and development</u>" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that to violate § 101 the claimed invention "must be <u>totally incapable</u> of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985)) states "<u>any</u> utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Id* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

As just <u>one</u> example of utility of the present nucleotide sequences, Applicants point out that, as taught in the specification as originally filed, at least at page 8, the claimed polynucleotide sequences can be used to track the expression of the genes encoding the described proteins. In particular, the specification describes how the described sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Such "DNA chips" clearly have

utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. Evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Agilent Technologies, Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value (net equity value of the transaction was $620 million) that it was acquired by large pharmaceutical company, Merck & Co., for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established.

The sequences of the present invention describe a *Notch* ligand and provide a unique identifier of the corresponding gene. Such gene chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, such as U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. The present nucleotide sequences clearly encode *Notch* ligands, as detailed throughout the specification, the utility of which are described directly and by incorporation by reference of issued U.S. Patent Nos. 5,786,158; 5,780,300 and 5,856,441, which describe uses for the *Notch* proteins and ligands. In addition, U.S. Patent No. 6,083,904 describes "Therapeutic and diagnostic methods and compositions of notch proteins and nucleic acids", and U.S. Patent No. 6,333,167, describes inhibitors of notch protein proteolysis. Issued U.S. Patents are presumed to be valid and to meet the requirements of 35 U.S.C. §§ 101, 102, 103 and 112, specifically, that they have utility, are novel, non-obvious, are enabled, meet the written description requirements and particularly point out and distinctly claim the invention. Therefore, this evidence appears to support Applicants' assertion that *Notch* proteins, ligands and antagonists have well -recognized utility.. In addition, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotides, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequences provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequences define how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of the Venter *et al.* article (Science, 2001, *291*:1304 *at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequences define biologically validated sequences that provide a unique and specific resource for mapping genome essentially as described in the Venter *et al.* article Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

As evidence of the credibility of Applicants assertion that the present invention is a *Notch* ligand, Applicants submit (as **Exhibit D**) an amino acid sequence comparison analysis between of SEQ ID NO:1 and Accession no. Q9UGD3, showing a 99.8% identity over the 506 amino acid overlap. Q9UGD3 (**Exhibit C**) has been annotated by third party scientists, wholly unaffiliated with Applicants, as encoding "Novel protein similar to SEL1L(Sel-1suppressor of lin-12, *C. elegans*)-like)" whose entire amino acid sequence in within the protein of the present invention.

Given this clear and convincing evidence that those of skill in the art would recognize the present invention as a *Notch* ligand. Clearly, there can be no question that Applicants' asserted utility for the described sequences is "credible." Therefore, the evidence clearly weighs in favor of Applicants' assertion that the presently described sequences have a specific, credible, and well-established utility.

Finally, Applicants respectfully submit that polymorphisms identified in the sequences of the present invention (at page 14, line 6-11) provide significant and specific utility as taught in the specification. Such polymorphisms have significant and specific utility in, *intra alia*, the fields of forensic science and human population biology. Such polymorphisms can also be used as specific markers useful, for example, in identifying human remains, determining human group migration patterns by identifying descendants of a specific group and in addition clearly the polymorphism of the present invention has significant and specific utility in resolving issues of paternity. Further, Applicants submit that these utilities are not only credible, but well established and known to those of skill in the art.

For each of the foregoing reasons, Applicants submit that the rejection of claims 1-6 under 35 U.S.C. § 101 have been overcome, and request that the rejection be withdrawn.

V. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects Claims 1-6 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description and enablement. Applicants respectfully traverse.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.*" *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the ... nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides comprising the nucleotide sequence of , for example, SEQ ID NO:1, or a nucleotide sequence that encodes SEQ ID NO:2, are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claims 1-6 thus meets the written description requirement.

The Action states, on page 7, line 10 in section 6.1:

"Even if the specification were enabling of how to use the NHP nucleic acid or polypeptide, enablement would not be found commensurate in scope with the claims. If one of skill in the art does not know how to use the nucleic acids or proteins the skilled artisan would clearly not know how to (use) a nucleic acid molecule that comprises 24 contiguous bases of nucleic acid sequence of SEQ ID NO:1."

Applicants respectfully disagree. The skilled artisan would easily recognize 24 contiguous nucleic acids derived from any of the nucleic acid sequences described in the sequence listing and would also know how to use a nucleic acid molecule that comprises 24 contiguous bases of nucleic acid sequence of SEQ ID NO:1. In fact, Applicants note that the entire DNA gene chip industry is based on the use of 24 or more contiguous bases of nucleic acid sequence. Therefore, Applicants submit that those of skill in the art would be able to make and use the present invention.

Having demonstrated that the present invention meets both the requirements for written description and enablement, Applicants respectfully submit that this rejection has been avoided and the argument rendered moot due to Applicants amendment of Claim 1 to read on the full length molecule.

For each of the foregoing reasons, Applicants submit that the rejection of Claims 1-6, and dependents, under 35 U.S.C. § 112, first paragraph, due to lack of written description has been overcome, and request that the rejection be withdrawn.

The Action also rejects claim 2, under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. As Claim 2 is not dependent on Claim 1, it is applicants belief that the Examiner intended to reject Claim 1 (rather than 2) in section 6.2 (Action at page 7).

As stated above, Applicants respectfully disagree. The skilled artisan would easily recognize 24 contiguous nucleic acids derived from any of the nucleic acid sequences described in the sequence listing and would also know how to use a nucleic acid molecule that comprises 24 contiguous bases of nucleic acid sequence of SEQ ID NO:1. In fact, Applicants note that the entire DNA gene chip industry is based on the use of 24 or more contiguous bases of nucleic acid sequence. Therefore, Applicants submit that those of skill in the art would be able to make and use the present invention.

Having indicated that the present invention meets both the requirements for written description and enablement, Applicants respectfully submit that this rejection has been avoided and this argument rendered moot due to Applicants amendment of Claim 1 to read on the full length molecule.

The Action next rejects Claim 1 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention. As Claim 1 does not describe hybridization, it is applicants belief that the Examiner intended to reject Claim 2 (rather than 1) in section 7.2 (Action at page 9). Therefore, the Action rejects Claim 2 as allegedly indefinite based on the term "stringent" hybridization conditions. While Applicants submit that the term is sufficiently definite, as a number of stringent hybridization conditions are defined in the specification and would be known to those of skill in the art, solely in order to progress the case more rapidly toward allowance, the claim has been revised, as suggested by the Examiner to omit the hybridization issue Thus, Applicants submit that rejection of Claim 2 under 35 U.S.C. § 112, second paragraph, has been avoided by amendment of Claim 2 and therefore respectfully request withdrawal of this rejection.

Based on the aforementioned points, Applicants submit that amended claims 1-6 meet both the requirements for written description and read on molecules of reasonable scope such that those skilled in the art would reasonably conclude that Applicants were in possession of the claimed invention at the time the application was filed.

VI. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing amendments and remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner O'Hara have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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Date

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